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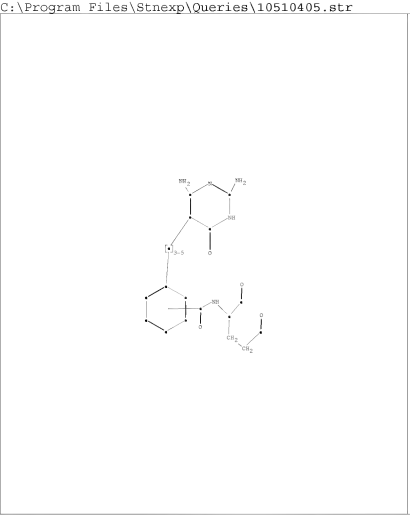

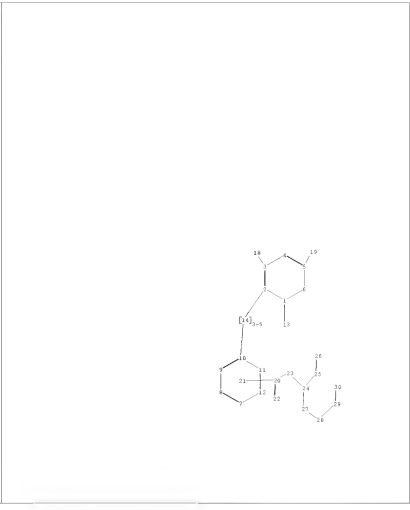

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ring nodes :
    1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
    1-13  2-14  3-18  5-19  10-14  20-22  20-23  23-24  24-25  24-27  25-26  27-28  28-29  29-30
ring bonds :
    1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-12  8-9  9-10  10-11  11-12
exact/norm bonds :
    1-2  1-6  1-13  2-3  3-4  3-18  4-5  5-6  5-19  20-22  20-23  23-24  25-26  29-30
exact bonds :
    2-14  10-14  24-25  24-27  27-28  28-29
normalized bonds :
    7-8  7-12  8-9  9-10  10-11  11-12
isolated ring systems :
    containing 1 : 7 :


Match level :
    1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom  11:Atom
    12:Atom  13:CLASS  14:CLASS  18:CLASS  19:CLASS  20:CLASS  21:Atom  22:CLASS  23:CLASS
    24:CLASS  25:CLASS  26:CLASS  27:CLASS  28:CLASS  29:CLASS  30:CLASS
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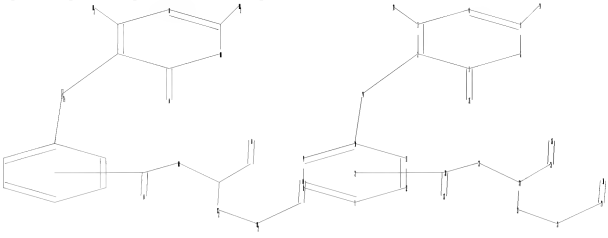

chain nodes :
13 14 18 19 20 22 23 24 25 26 27 28 29 30
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
1-13 2-14 3-18 5-19 10-14 20-22 20-23 23-24 24-25 24-27 25-26 27-28
28-29 29-30
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-6 1-13 2-3 3-4 3-18 4-5 5-6 5-19 20-22 20-23 23-24 25-26 29-30
exact bonds :
2-14 10-14 24-25 24-27 27-28 28-29
normalized bonds :
7-8 7-12 8-9 9-10 10-11 11-12
isolated ring systems :
containing 1 : 7 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 18:CLASS 19:CLASS 20:CLASS 21:Atom
22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS
30:CLASS

L1 STRUCTURE UPLOADED

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=> d l1
L1 HAS NO ANSWERS
L1                STR
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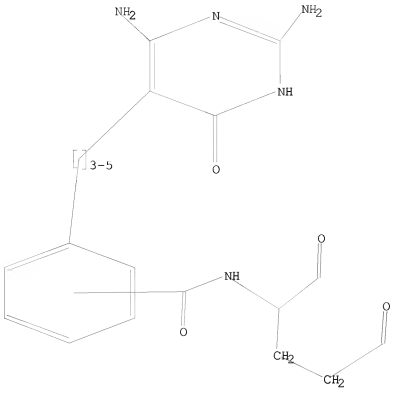


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Structure attributes must be viewed using STN Express query preparation.


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SAMPLE IS IGNORED AS A SCOPE FOR THIS SEARCH
L2          740 1L

=> s l1 sss sam
SAMPLE SEARCH INITIATED 12:11:07 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        6 TO ITERATE

100.0% PROCESSED         6 ITERATIONS                                  3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE   **COMPLETE**
                        BATCH    **COMPLETE**
PROJECTED ITERATIONS:             6 TO      266
PROJECTED ANSWERS:                3 TO      163

L3            3 SEA SSS SAM L1

=> => s l1 sss ful
FULL SEARCH INITIATED 12:11:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      124 TO ITERATE
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100.0% PROCESSED 124 ITERATIONS 87 ANSWERS
SEARCH TIME: 00.00.01

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L5 27 L4

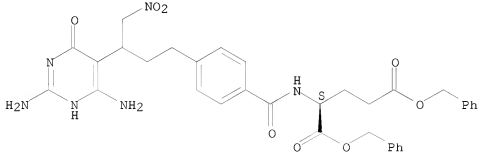
=> d l5 1-27 bib,ab,hitstr

L5 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:2239 CAPLUS
DN 146:122294
TI Method for preparation of folic acid antagonist and its intermediate
IN Cen, Junda; Lu, Aifeng
PA Jiangsu Hansoh Pharmaceutical Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 8pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1880316	A	20061220	CN 2005-10078426	20050615
PRAI CN 2005-10078426		20050615		

OS CASREACT 146:122294; MARPAT 146:122294
AB The title folic acid antagonist N-(4-[2-(2-amine-4(3H)-oxy-7H-pyrrole di[2,3-d]pyridine-5-yl)ethyl]benzoyl)-L-glutamic acid or its pharmaceutical salt is represented by structure I. The intermediate of folic acid antagonist is dibenzyl N-(4-[2-(2-amine-4(3H)-oxy-7H-pyrrole di[2,3-d]pyridine-5-yl)ethyl]benzoyl)-L-glutamate. The title method comprises carrying out catalytic hydrogenation of compound II (R and R1 = H, halogen, or C1-4 alkyl) under the catalysis of metal catalyst.
IT 909795-98-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of folic acid antagonist and its intermediate)
RN 909795-98-8 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoyl]-, 1,5-bis(phenylmethyl) ester (CA INDEX NAME)

Absolute stereochemistry.

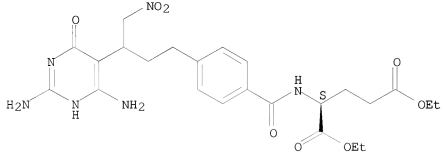


L5 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:939973 CAPLUS
DN 145:336315
TI Process for preparation of nitro compounds as intermediates for synthesizing pemetrexed
IN Lin, Dong; Fan, Chuanwen; Zhu, Yidong; Wang, Jingyi; Zhang, Minghui; Dai, Lianhua
PA Hainan Tianyuan Kangze Pharmaceutical Science and Technology Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 11pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1827604	A	20060906	CN 2006-10043441	20060406
PRAI CN 2006-10043441		20060406		

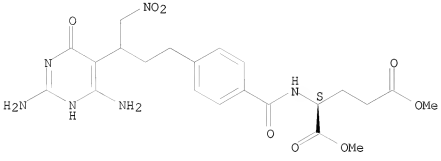
OS CASREACT 145:336315; MARPAT 145:336315
AB The invention provides a process for preparing nitro compds. I [wherein R1 and R2 = independently H or carboxy protecting group] as intermediates for synthesizing pemetrexed. For example, Me 4-(3-hydroxy-4-nitrobutyl)benzoate was hydrolyzed in the presence of sodium hydroxide, followed by reacting with di-Et L-glutamate hydrochloride and dehydration with mesyl chloride to give di-Et N-[4-(4-nitro-3-butenyl)benzoyl]-L-glutamate. The glutamate obtained in the previous step was reacted with 2,4-diamino-6-hydroxypyrimidine in a mixture of Et acetate and water to give II. II can be treated with acids or bases to give pemetrexed, which is a useful antitumor agent.
IT 907182-47-2P 909795-96-6P 909795-98-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of nitro compds. as intermediates for synthesizing pemetrexed)
RN 907182-47-2 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoyl]-, diethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



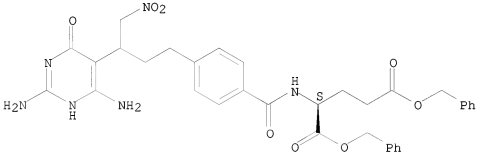
RN 909795-96-6 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoyl]-, dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 909795-98-8 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoyl]-, 1,5-bis(phenylmethyl) ester (CA INDEX NAME)

Absolute stereochemistry.

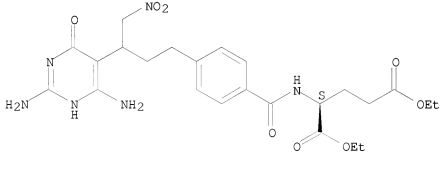


L5 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:538395 CAPLUS
DN 145:272017
TI Preparation of anticancer N-(pyrrolo[2,3-d]pyrimidin-5-yl)carbonylglutamate derivatives
IN Luo, Jie; Ye, Wenrun; Deng, Jie; Zhou, Yongchun
PA Chongqing Pharmaceutical Research Institute Co., Ltd., Peop. Rep. China; Shanghai Clonbiotech Co., Ltd.
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 18 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN 1778797	A	20060531	CN 2004-10097284	20041125
PRAI CN 2004-10097284		20041125		

OS MARPAT 145:272017
AB Title compds., e.g. Pemetrexed, are prepared Thus, Pemetrexed was prepared in 35% overall yield from Et 4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoate by hydrolysis, condensation with with glutamic acid di-Et ester hydrochloride, hydrolysis, reduction, and cyclization.
IT 907182-47-2P 907182-48-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of anticancer N-(pyrrolo[2,3-d]pyrimidin-5-yl)carbonylglutamate derivs.)
RN 907182-47-2 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoyl]-, diethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

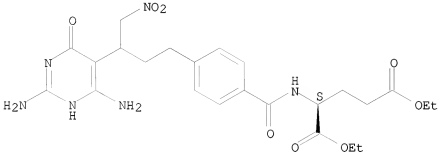


RN 907182-48-3 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-4-nitrobutyl]benzoyl]-, diethyl ester, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)

CM 1

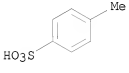
CRN 907182-47-2
CMF C24 H32 N6 O8

Absolute stereochemistry.



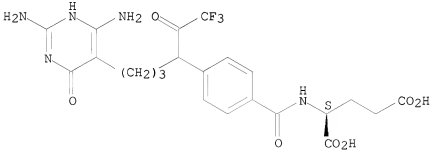
CM 2

CRN 104-15-4
CMF C7 H8 O3 S



L5 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:349589 CAPLUS
DN 145:20642
TI Discovery of a Potent, Nonpolyglutamatable Inhibitor of Glycinamide Ribonucleotide Transformylase
AU DeMartino, Jessica K.; Hwang, Inkyu; Xu, Lan; Wilson, Ian A.; Boger, Dale L.
CS Departments of Chemistry Molecular Biology and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Journal of Medicinal Chemistry (2006), 49(10), 2998-3002
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 145:20642
AB Glycinamide ribonucleotide transformylase (GAR Tfase) catalyzes the first of two formyl transfer steps in the de novo purine biosynthetic pathway that require folate cofactors. Herein we report the discovery of a potent, nonpolyglutamatable, and selective inhibitor of GAR Tfase. Compound 12, which possesses a tetrazole in place of the γ-carboxylic acid in the L-glutamate subunit of the potent GAR Tfase inhibitor 1, was active in cellular-based functional assays exhibiting purine-sensitive cytotoxic activity (IC50 = 40 nM, CCRF-CEM) and was selective for inhibition of rhGAR Tfase (Ki = 130 nM). Notably, 12 was only 2.5-fold less potent than 1 in cellular assays and 4-fold less potent against rhGAR Tfase. Like 1, this functional activity of 12 in the cell-based assay benefits from and requires transport into the cell by the reduced folate carrier but, unlike 1, is independent of folyl polyglutamate synthase (FPGS) expression levels and polyglutamation.
IT 553681-09-7DP, derivs.
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nonpolyglutamatable inhibitors of glycinamide ribonucleotide tansformylase)
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

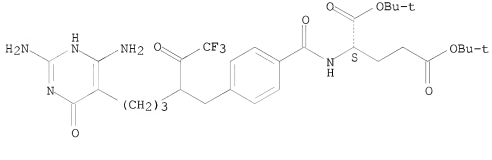
Absolute stereochemistry.



RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:354191 CAPLUS
DN 143:19440
TI Synthesis and biological evaluation of N-{4-[5-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-2-(2,2,2-trifluoroacetyl)pentyl]benzoyl}--glutamic acid as a potential inhibitor of GAR Tfase and the de novo purine biosynthetic pathway
AU Cheng, Heng; Hwang, Inkyu; Chong, Youhoon; Tavassoli, Ali; Webb, Michael E.; Zhang, Yan; Wilson, Ian A.; Benkovic, Stephen J.; Boger, Dale L.
CS Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (2005), 13(10), 3593-3599
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Ltd.
DT Journal
LA English
OS CASREACT 143:19440
AB The synthesis and evaluation of N-{4-[5-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-2-(2,2,2-trifluoroacetyl)pentyl]benzoyl}--glutamic acid (I) as an inhibitor of glycinamide ribonucleotide transformylase (GAR Tfase) and aminoimidazole carboxamide ribonucleotide transformylase (AICAR Tfase) are reported. The inhibitor I was prepared in a convergent synthesis involving C-alkylation of Me 4-(4,4,4-trifluoro-3-dimethylhydrazonobutyl)benzoate with 1-chloro-3-iodopropane followed by construction of the pyrimidinone ring. Compound I was found to be an effective inhibitor of recombinant human GAR Tfase (Ki = 0.50 μM), whereas it was inactive (Ki > 100 μM) against E. coli GAR Tfase as well as recombinant human AICAR Tfase. Compound I exhibited modest, purine-sensitive growth inhibitory activity against the CCRF-CEM cell line (IC50 = 6.0 μM).
IT 914262-53-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(inhibitors; synthesis and biol. evaluation of N-{4-[5-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-2-(2,2,2-trifluoroacetyl)pentyl]benzoyl}-L-glutamic acid as a potential inhibitor of GAR Tfase and the de novo purine biosynthetic pathway)
RN 914262-53-6 CAPLUS
CN L-Glutamic acid, N-[4-[5-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)-2-(trifluoroacetyl)pentyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



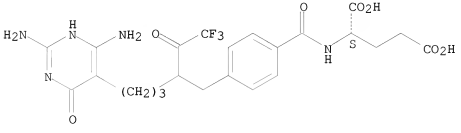
IT 914263-00-6

RL: PAC (Pharmacological activity); BIOL (Biological study)
(synthesis and biol. evaluation of N-{4-[5-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-2-(2,2,2-trifluoroacetyl)pentyl]benzoyl}-L-glutamic acid as a potential inhibitor of GAR Tfase and the de novo purine biosynthetic pathway)

RN 914263-00-6 CAPLUS

CN L-Glutamic acid, N-[4-[5-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-2-(trifluoroacetyl)pentyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



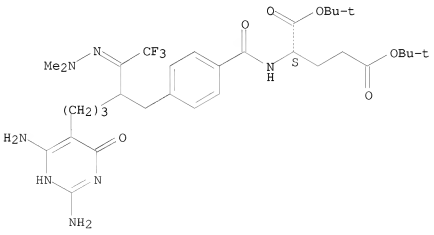
IT 852812-71-6P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and biol. evaluation of N-{4-[5-(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-2-(2,2,2-trifluoroacetyl)pentyl]benzoyl}-L-glutamic acid as a potential inhibitor of GAR Tfase and the de novo purine biosynthetic pathway)

RN 852812-71-6 CAPLUS

CN L-Glutamic acid, N-[4-[5-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-2-[1-(dimethylhydrazono)-2,2,2-trifluoroethyl]pentyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

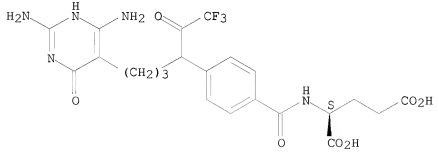


RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:354190 CAPLUS
DN 143:616
TI Synthesis and biological evaluation of α- and γ-carboxamide derivatives of 10-CF3CO-DDACTHF
AU Chong, Youhoon; Hwang, Inkyu; Tavassoli, Ali; Zhang, Yan; Wilson, Ian A.; Benkovic, Stephen J.; Boger, Dale L.
CS Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (2005), 13(10), 3587-3592
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Ltd.
DT Journal
LA English
OS CASREACT 143:616
AB Structurally-related, but non-polyglutamylatable, derivs. of 10-CF3CO-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid, 10-CF3CO-DDACTHF (I), where X = Glu, Gln and isoGln, were prepared and evaluated as inhibitors of recombinant human (rh) GAR Tfase. While the -glutamate α-carboxamide derivative (III)(=I: X=isoGln) was much less effective as a rhGAR Tfase inhibitor (Ki = 4.8 μM) and inactive in cellular functional assays, the γ-carboxamide derivative (II) (=I: X=Gln) was found to be a potent and selective rhGAR Tfase inhibitor (Ki = 0.056 μM) being only 4-fold less potent than (I: X=Glu) (Ki = 0.015 μM). Moreover, II was effective in cellular functional assays exhibiting purine sensitive cytotoxic activity (IC50 = 300 nM, CCRF-CEM) only 20-fold less potent than I: X=Glu (IC50 = 16 nM), consistent with inhibition of de novo purine biosynthesis via selective inhibition of GAR Tfase. Like I: X=Glu, II is transported into the cell by the reduced folate carrier. Unlike I: X=Glu, the functional activity of II is not dependent upon FPGS polyglutamylation.
IT 553681-09-7, 10-(Trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic Acid
RL: PAC (Pharmacological activity); BIOL (Biological study)
(synthesis and biol. evaluation of α- and γ-carboxamide derivs. of 10-CF3CO-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF3CO-DDACTHF) as ribonucleotide transformylase inhibitors)
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



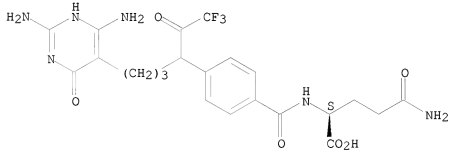
IT 852415-96-4P 852415-97-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and biol. evaluation of α- and γ-carboxamide derivs. of 10-CF3CO-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF3CO-DDACTHF) as ribonucleotide transformylase inhibitors)

RN 852415-96-4 CAPLUS

CN L-Glutamine, N2-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

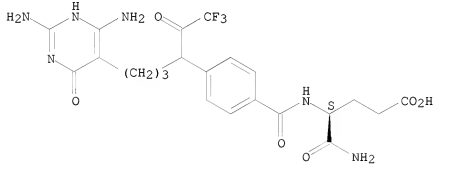
Absolute stereochemistry.



RN 852415-97-5 CAPLUS

CN Pentanoic acid, 5-amino-4-[[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]amino]-5-oxo-, (4S)- (9CI) (CA INDEX NAME)

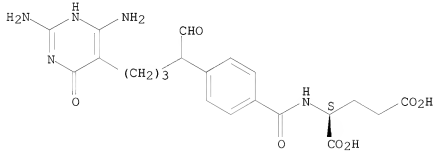
Absolute stereochemistry.



RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

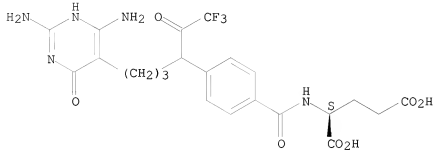
L5 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:354188 CAPLUS
DN 143:615
TI Design, synthesis, and biological evaluation of 10-methanesulfonyl-DDACTHF, 10-methanesulfonyl-5-DACTHF, and 10-methylthio-DDACTHF as potent inhibitors of GAR Tfase and the de novo purine biosynthetic pathway
AU Cheng, Heng; Chong, Youhoon; Hwang, Inkyu; Tavassoli, Ali; Zhang, Yan; Wilson, Ian A.; Benkovic, Stephen J.; Boger, Dale L.
CS Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (2005), 13(10), 3577-3585
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Ltd.
DT Journal
LA English
OS CASREACT 143:615
AB The synthesis and evaluation of 10-methanesulfonyl-DDACTHF (I, RX = MeSO2CH2) (II), 10-methanesulfonyl-5-DACTHF I, (R = MeSO2N) (III), and 10-methylthio-DDACTHF I, RX = MeSCH2 (IV) as potential inhibitors of glycinamide ribonucleotide transformylase (GAR Tfase) and aminoimidazole carboxamide ribonucleotide transformylase (AICAR Tfase) are reported. II (Ki = 0.23 μM), III (Ki = 0.58 μM), and 10-methylthio-DDACTHF IV (Ki = 0.25 μM) were found to be selective and potent inhibitors of recombinant human GAR Tfase. Of these, IV exhibited exceptionally potent, purine sensitive growth inhibition activity (3, IC50 = 100 nM) against the CCRF-CEM cell line being 3-fold more potent than Lometrexol and 30-fold more potent than the parent, unsubstituted DDACTHF, whereas II and III exhibited more modest growth inhibition activity: II, IC50 = 1.0 μM and III, IC50 = 2.0 μM.
IT 485389-59-1 553681-09-7
RL: PAC (Pharmacological activity); BIOL (Biological study)
(design, synthesis, and biol. evaluation of methylthio dideaza-acyclic tetrahydrofolic acid derivs. as potent inhibitors of GAR Tfase and de novo purine biosynthetic pathway)
RN 485389-59-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



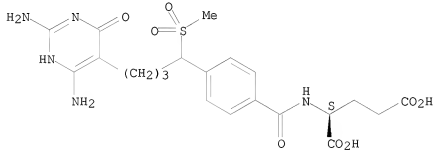
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



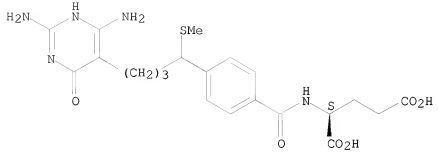
IT 852475-20-8P 852475-24-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design, synthesis, and biol. evaluation of methylthio dideaza-acyclic tetrahydrofolic acid derivs. as potent inhibitors of GAR Tfase and de novo purine biosynthetic pathway)
RN 852475-20-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(methylsulfonyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 852475-24-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(methylthio)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

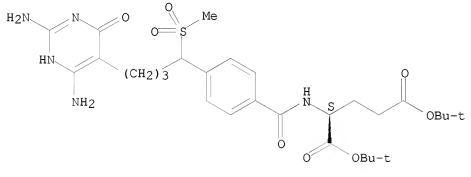


IT 852475-41-3P 852475-60-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design, synthesis, and biol. evaluation of methylthio dideaza-acyclic tetrahydrofolic acid derivs. as potent inhibitors of GAR Tfase and de novo purine biosynthetic pathway)

RN 852475-41-3 CAPLUS

CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(methylsulfonyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

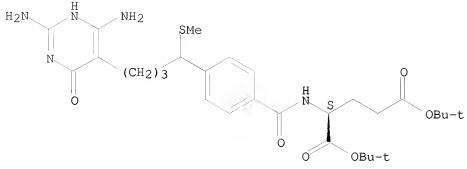
Absolute stereochemistry.



RN 852475-60-6 CAPLUS

CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(methylthio)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



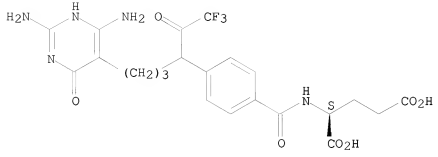
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:837053 CAPLUS
DN 139:338192
TI Preparation of folate analogs as inhibitors of glycinamide ribonucleotide transformylase
IN Boger, Dale L.
PA The Scripps Research Institute, USA
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
Applicant's
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003087065	A1	20031023	WO 2003-US10944	20030407
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2481344	A1	20031023	CA 2003-2481344	20030407
	AU 2003234705	A1	20031027	AU 2003-234705	20030407
	EP 1495006	A1	20050112	EP 2003-728361	20030407
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2005528397	T	20050922	JP 2003-584021	20030407
	US 2007167377	A1	20070719	[redacted]	20050504
PRAI	US 2002-370591P	P	20020405		
	WO 2003-US10944	W	20030407		

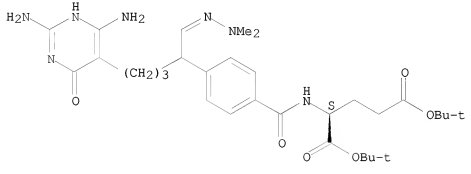
OS MARPAT 139:338192
AB Glutamic acid derivs. I [R1 is CHO, CH2OH, CH:NNMe2, COCF3, or CH(OH)CF3; R2, R3 are OH, OBu-t, glutamyl, or oligoglutamyl (with provisos)] were prepared as potent inhibitors of human glycinamide ribonucleotide transformylase (GAR Tfase) and aminoimidazole carboxamide ribonucleotide transformylase (ALCAR Tfase). Thus, folate analog I (R1 = COCF3, R2 = R3 = OH) (10-CF3CO-DDACTHF) was prepared, assayed for inhibition of GAR Tfase and cytotoxicity, and the crystal structure of its complex with GAR Tfase determined
IT 553681-09-7DP, complex with GAR Tfase
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and crystal structure of folate analog complex with GAR Tfase)
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



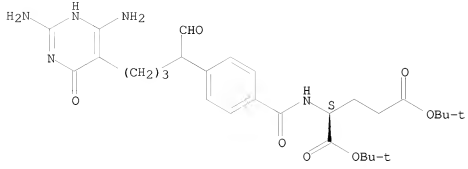
IT 485389-64-8P 485389-65-9P 485389-73-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of folate analogs as inhibitors of glycinamide ribonucleotide transformylase)
RN 485389-64-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 485389-65-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

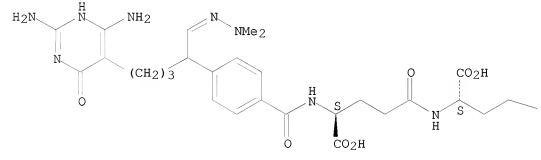
Absolute stereochemistry.



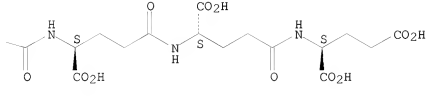
RN 485389-73-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

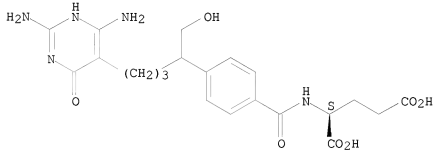


IT 136527-62-3P 485389-59-1P 485389-67-1P
485389-68-2P 485389-72-8P 485389-76-2P
485389-77-3P 553681-09-7P 553681-10-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of folate analogs as inhibitors of glycinamide ribonucleotide transformylase)

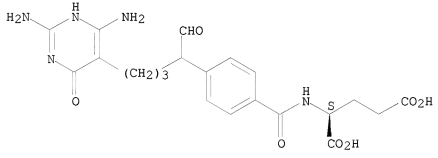
RN 136527-62-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



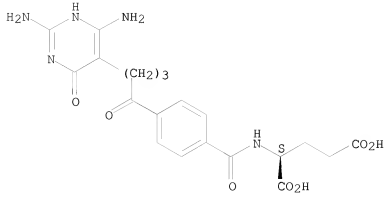
RN 485389-59-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



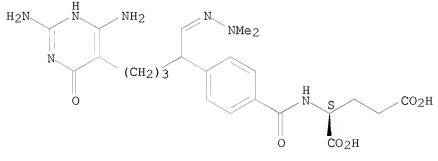
RN 485389-67-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-oxobutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 485389-68-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]- (9CI) (CA INDEX NAME)

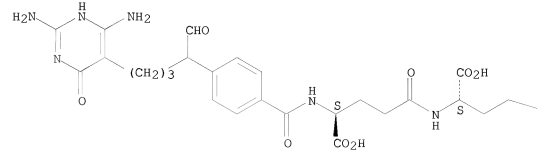
Absolute stereochemistry.
Double bond geometry unknown.



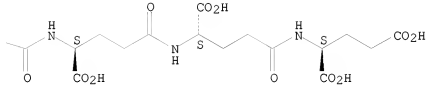
RN 485389-72-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



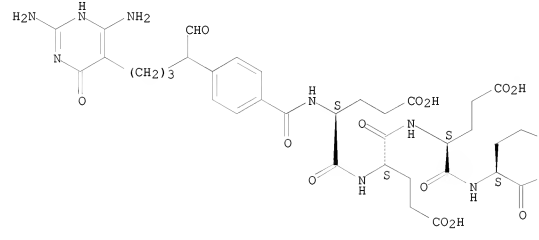
PAGE 1-B



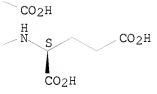
RN 485389-76-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



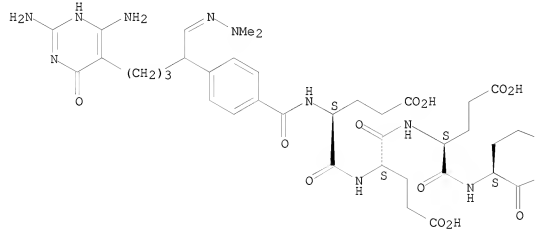
PAGE 1-B

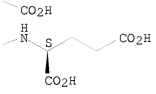


RN 485389-77-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

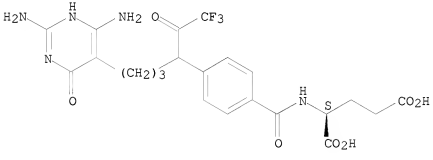
PAGE 1-A





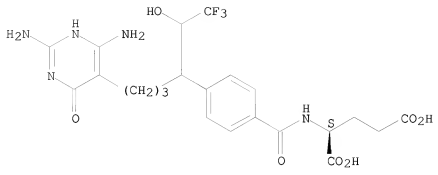
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 553681-10-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(2,2,2-trifluoro-1-hydroxyethyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

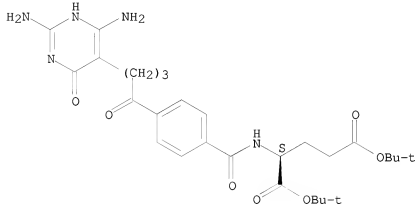


IT 485389-66-0P 485389-69-3P 485389-70-6P
485389-71-7P 485389-75-1P 553681-17-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of folate analogs as inhibitors of glycinamide ribonucleotide transformylase)

RN 485389-66-0 CAPLUS

CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-oxobutyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

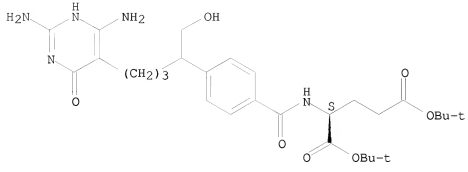
Absolute stereochemistry.



RN 485389-69-3 CAPLUS

CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

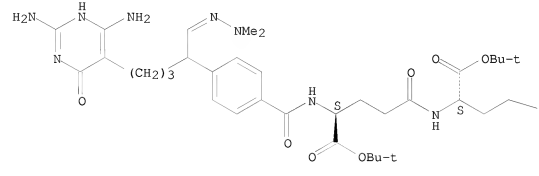
Absolute stereochemistry.



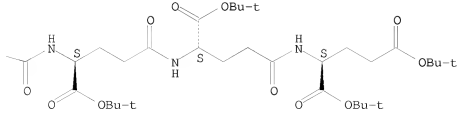
RN 485389-70-6 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



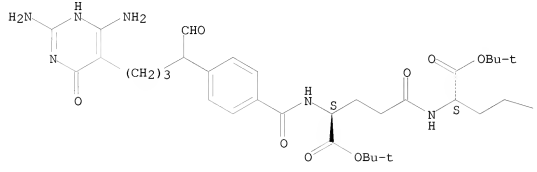
PAGE 1-B



RN 485389-71-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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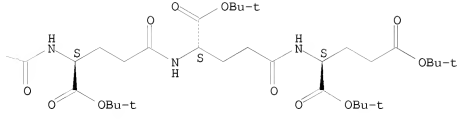
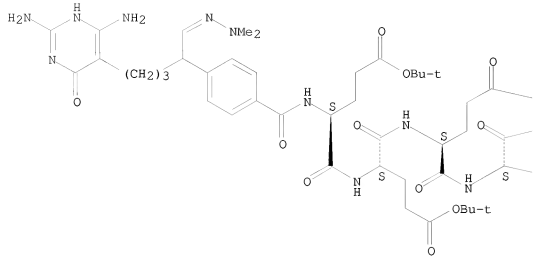


RN 485389-75-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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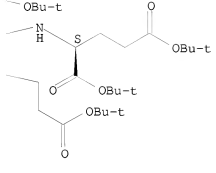
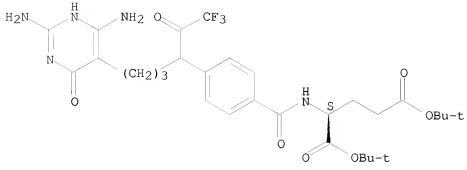


RN 553681-17-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

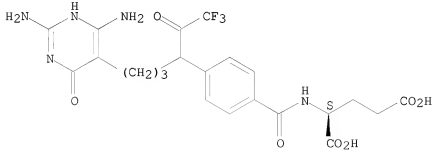


RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:728117 CAPLUS
DN 140:111368
TI Design, synthesis and biological evaluation of 10-CF3CO-DDACTHF analogues and derivatives as inhibitors of GAR Tfase and the de novo purine biosynthetic pathway
AU Desharnais, Joel; Hwang, Inkyu; Zhang, Yan; Tavassoli, Ali; Baboval, Justin; Benkovic, Stephen J.;
CS Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (2003), 11(20), 4511-4521
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 140:111368
AB The synthesis and evaluation of analogs and key derivs. of 10-CF3CO-DDACTHF, the pyrimidinone analog of DDATHF (DDATHF = 5,10-dideazatetrahydrofolate, Lometrexol), as inhibitors of glycinamide ribonucleotide transformylase (GAR Tfase) and aminoimidazole carboxamide transformylase (AICAR Tfase) are reported. Polyglutamates I (n = 1 - 5; R = F3CCO, F3CCHOH, HO2C) were synthesized and evaluated as inhibitors of Escherichia coli and recombinant human (rh) GAR Tfase, and AICAR Tfase. Although the pentaglutamate I (n = 5; R = F3CCO) was found to be the most active inhibitor of the series tested against rhGAR Tfase (Ki = 0.004 μM), little distinction between the mono-pentaglutamate derivs. was observed (Ki = 0.02-0.004 μM), suggesting that the principal role of the required polyglutamation of I is intracellular retention. In contrast, I (n = 1 - 5; R = F3CCO) were much less inactive when tested against rhAICAR Tfase (Ki = 65-0.120 μM) and very selective (≥100-fold) for rh vs. E. coli GAR Tfase. I (n = 1; R = HO2C) was found to be much less active (1000-fold).
IT 553681-09-7 553681-10-0
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(preparation of polyglutamate-derived diaminopyrimidinones, their cytotoxicity and glycinamide ribonucleotide transformylase and aminoimidazole carboxamide transformylase inhibiting activity)
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

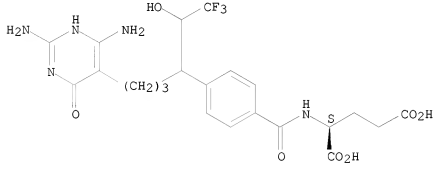
common inventors
published October 2003

Absolute stereochemistry.



RN 553681-10-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(2,2,2-trifluoro-1-hydroxyethyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



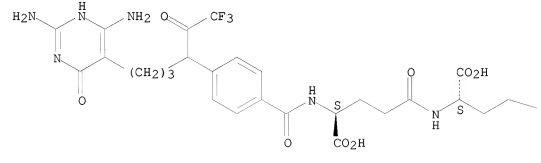
IT 647833-25-8P 647833-28-1P 647833-32-7P
647833-35-0P 647833-38-3P 647833-48-5P
647833-60-1P
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of polyglutamate-derived diaminopyrimidinones, their cytotoxicity and glycinamide ribonucleotide transformylase and aminoimidazole carboxamide transformylase inhibiting activity)
RN 647833-25-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 647833-24-7
CMF C27 H31 F3 N6 O10

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

CM 2

CRN 76-05-1
CMF C2 H F3 O2

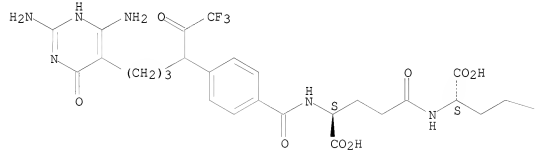
RN 647833-28-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

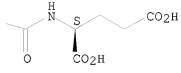
CRN 647833-27-0
CMF C32 H38 F3 N7 O13

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



CM 2

CRN 76-05-1
CMF C2 H F3 O2

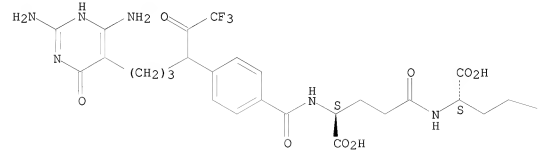
RN 647833-32-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 647833-31-6
CMF C37 H45 F3 N8 O16

Absolute stereochemistry.

PAGE 1-A



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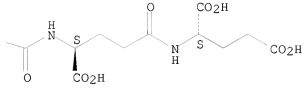


CM 2

CRN 76-05-1
CMF C2 H F3 O2

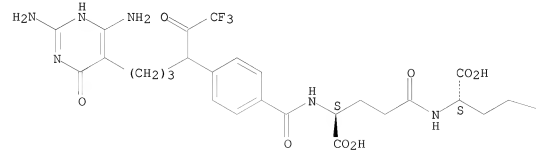
RN 647833-35-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 647833-34-9
CMF C42 H52 F3 N9 O19

Absolute stereochemistry.

PAGE 1-A



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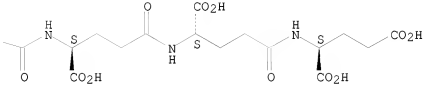


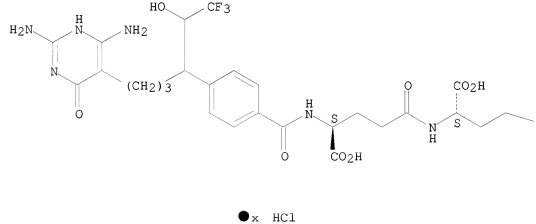
CM 2

CRN 76-05-1
CMF C2 H F3 O2

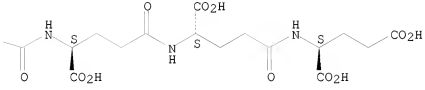
RN 647833-38-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(2,2,2-trifluoro-1-hydroxyethyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



●x HCl

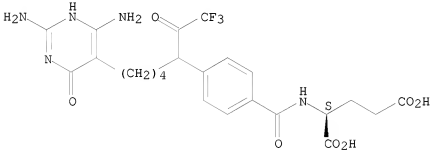


RN 647833-48-5 CAPLUS
CN L-Glutamic acid, N-[4-[5-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)pentyl]benzoyl]-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 647833-47-4
CMF C23 H26 F3 N5 O7

Absolute stereochemistry.



CM 2

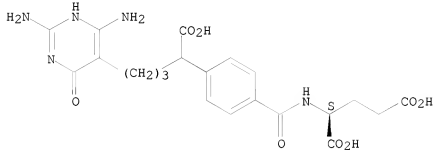
CRN 76-05-1
CMF C2 H F3 O2

RN 647833-60-1 CAPLUS
CN L-Glutamic acid, N-[4-[1-carboxy-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 647833-59-8
CMF C21 H25 N5 O8

Absolute stereochemistry.



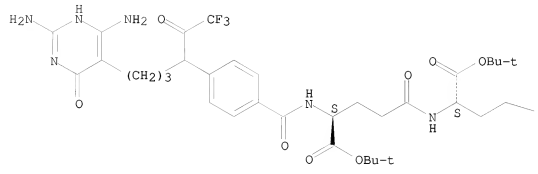
CM 2

CRN 76-05-1
CMF C2 H F3 O2

IT 647833-15-6P 647833-17-8P 647833-20-3P
647833-22-5P 647833-45-2P 647833-58-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of polyglutamate-derived diaminopyrimidinones, their cytotoxicity and glycinamide ribonucleotide transformylase and aminoimidazole carboxamide transformylase inhibiting activity)
RN 647833-15-6 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-, tris(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

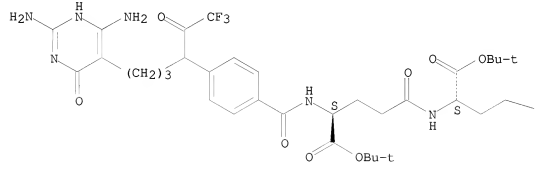


PAGE 1-B

RN 647833-17-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-, tetrakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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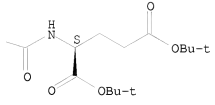
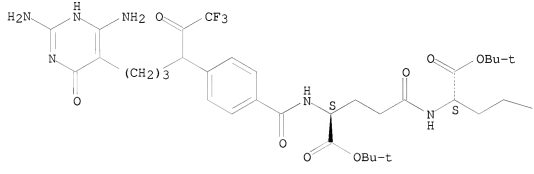


RN 647833-20-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, pentakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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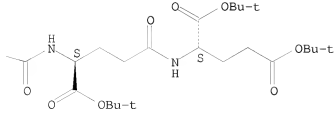
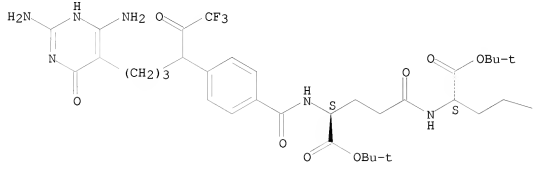


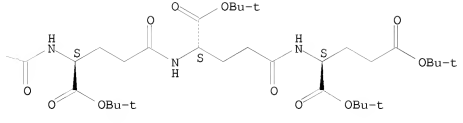
RN 647833-22-5 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

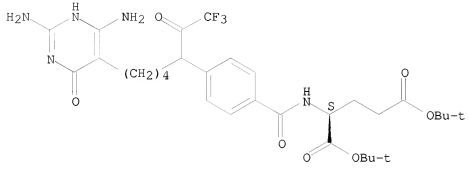


PAGE 1-B



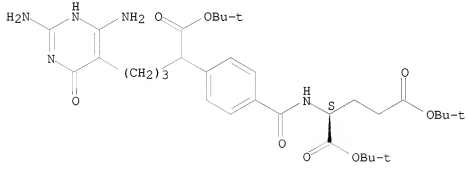
RN 647833-45-2 CAPLUS
CN L-Glutamic acid, N-[4-[5-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)pentyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 647833-58-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(1,1-dimethylethoxy)carbonyl]butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

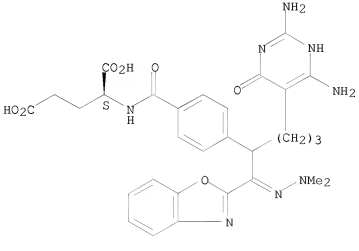


RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:728116 CAPLUS
DN 140:122083
TI 10-(2-Benzoxazolcarbonyl)-5,10-dideaza-acyclic-5,6,7,8-tetrahydrofolic acid. A potential inhibitor of GAR transformylase and AICAR transformylase
AU Marsilje, Thomas H.; Hedrick, Michael P.; Desharnais, Joel; Capps, Kevin; Tavassoli, Ali; Zhang, Yan; Benkovic, Stephen J.;
CS Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (2003) 11(20), 4503-4509
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 140:122083
AB The design and synthesis of 10-(2-benzoxazolcarbonyl)-DDACTHF (I) as an inhibitor of glycinamide ribonucleotide transformylase (GAR Tfase) and aminoimidazole carboxamide transformylase (AICAR Tfase) are reported. Ketone I and the corresponding alc. were evaluated for inhibition of GAR Tfase and AICAR Tfase and the former was found to be a potent inhibitor of recombinant human (rh) GAR Tfase (Ki=600 nM).
IT 648908-83-2P 648908-85-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of a folate analog as potential inhibitor of GAR transformylase and AICAR transformylase)
RN 648908-83-2 CAPLUS
CN L-Glutamic acid, N-[4-[1-[2-benzoxazolyl(dimethylhydrazono)methyl]-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

common inventors
published October 2003

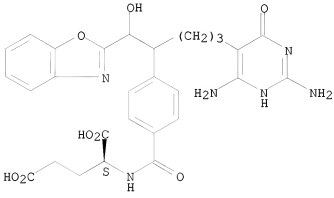
Absolute stereochemistry.
Double bond geometry unknown.



RN 648908-85-4 CAPLUS
CN L-Glutamic acid, N-[4-[1-(2-benzoxazolylhydroxymethyl)-4-(2,6-diamino-1,4-

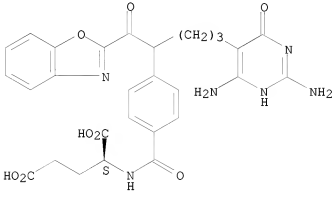
dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



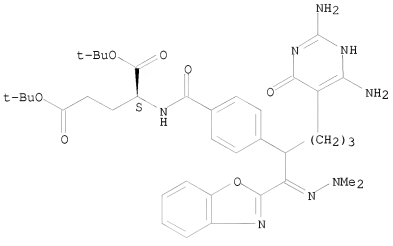
IT 648908-75-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of a folate analog as potential inhibitor of GAR transformylase and AICAR transformylase)
RN 648908-75-2 CAPLUS
CN L-Glutamic acid, N-[4-[1-(2-benzoxazolylcarbonyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



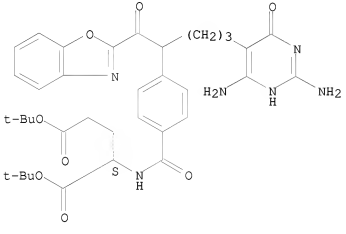
IT 648908-82-1P 648908-84-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of a folate analog as potential inhibitor of GAR transformylase and AICAR transformylase)
RN 648908-82-1 CAPLUS
CN L-Glutamic acid, N-[4-[1-[2-benzoxazolyl(dimethylhydrazono)methyl]-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 648908-84-3 CAPLUS
CN L-Glutamic acid, N-[4-[1-(2-benzoxazolylcarbonyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

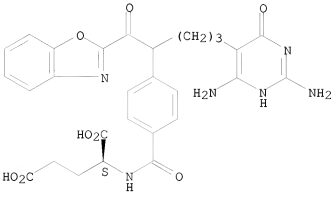


IT 648908-90-1P 648908-92-3P 648908-93-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of a folate analog as potential inhibitor of GAR transformylase and AICAR transformylase)
RN 648908-90-1 CAPLUS
CN L-Glutamic acid, N-[4-[1-(2-benzoxazolylcarbonyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 648908-75-2
CMF C28 H28 N6 O8

Absolute stereochemistry.



CM 2

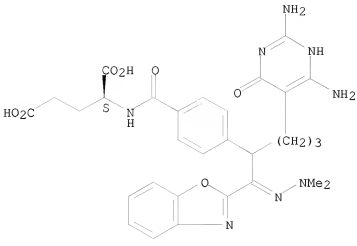
CRN 76-05-1
CMF C2 H F3 O2

RN 648908-92-3 CAPLUS
CN L-Glutamic acid, N-[4-[1-[2-benzoxazolyl(dimethylhydrazono)methyl]-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 648908-83-2
CMF C30 H34 N8 O7

Absolute stereochemistry.
Double bond geometry unknown.

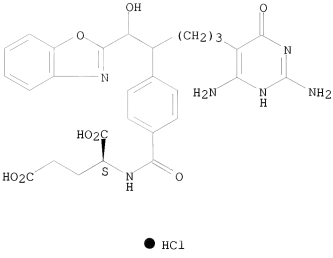


CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 648908-93-4 CAPLUS
CN L-Glutamic acid, N-[4-[1-(2-benzoxazolylhydroxymethyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

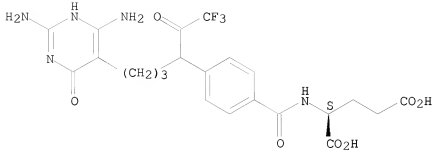


RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:340396 CAPLUS
DN 139:81192
TI Rational Design, Synthesis, Evaluation, and Crystal Structure of a Potent Inhibitor of Human GAR Tfase: 10-(Trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic Acid
AU Zhang, Yan; Desharnais, Joel; Marsilje, Thomas H.; Li, Chenglong; Hedrick, Michael P.; Gooljarsingh, Lata T.; Tavassoli, Ali; Benkovic, Stephen J.; Olson, Arthur J.
CS Departments of Molecular Biology and Chemistry and The Skaggs Institute for Chemical Biology, Scripps Research Institute, La Jolla, CA, 92037, USA
SO Biochemistry (2003), 42(20), 6043-6056
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
OS CASREACT 139:81192
AB Glycinamide ribonucleotide transformylase (GAR Tfase) has been the target of anti-neoplastic intervention for almost two decades. Here, we use a structure-based approach to design a novel folate analog, 10-(trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF3CO-DDACTHF, 1), which specifically inhibits recombinant human GAR Tfase (Ki = 15 nM), but is inactive (Ki > 100 μM) against other folate-dependent enzymes that have been examined Moreover, compound 1 is a potent inhibitor of tumor cell proliferation (IC50 = 16 nM, CCRF-CEM), which represents a 10-fold improvement over Lometrexol, a GAR Tfase inhibitor that has been in clin. trials. Thus, this folate analog 1 is among the most potent and selective inhibitors known toward GAR Tfase. Contributing to its efficacious activity, compound 1 is effectively transported into the cell by the reduced folate carrier and intracellularly sequestered by polyglutamation. The crystal structure of human GAR Tfase with folate analog 1 at 1.98 Å resolution represents the first structure of any GAR Tfase to be determined with a cofactor or cofactor analog without the presence of substrate. The folate-binding loop of residues 141-146, which is highly flexible in both Escherichia coli and unliganded human GAR Tfase structures, becomes highly ordered upon binding 1 in the folate-binding site. Computational docking of the natural cofactor into this and other apo or complexed structures provides a rational basis for modeling how the natural cofactor 10-formyltetrahydrofolic acid interacts with GAR Tfase, and suggests that this folate analog-bound conformation represents the best template to date for inhibitor design.
IT 553681-09-7P 553681-10-0P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(crystal structure and tumor cell cytotoxicity of glycinamide ribonucleotide transformylase (GAR Tfase) inhibitor 10-(trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF3CO-DDACTHF))
RN 553681-09-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

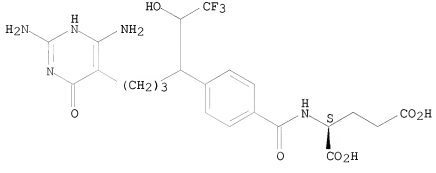
Absolute stereochemistry.

common inventors
published May 2003



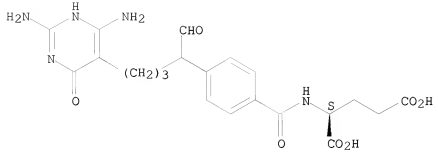
RN 553681-10-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(2,2,2-trifluoro-1-hydroxyethyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



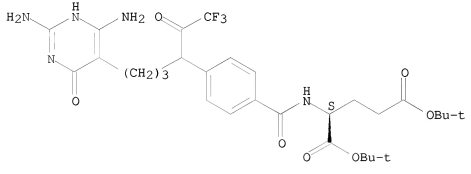
IT 485389-59-1
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal structure and tumor cell cytotoxicity of glycinamide ribonucleotide transformylase (GAR Tfase) inhibitor 10-(trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF3CO-DDACTHF))
RN 485389-59-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 553681-17-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(crystal structure and tumor cell cytotoxicity of glycinamide ribonucleotide transformylase (GAR Tfase) inhibitor 10-(trifluoroacetyl)-5,10-dideazaacyclic-5,6,7,8-tetrahydrofolic acid (10-CF3CO-DDACTHF))
RN 553681-17-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(trifluoroacetyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

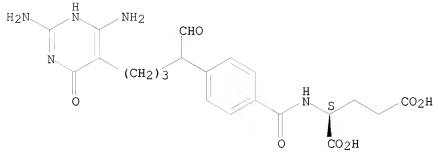
Absolute stereochemistry.



RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

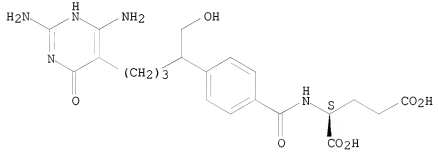
L5 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:418357 CAPLUS
DN 138:100419
TI 10-Formyl-5,10-dideaza-acyclic-5,6,7,8-tetrahydrofolic acid (10-Formyl-DDACTHF) A potent cytotoxic agent acting by selective inhibition of human GAR Tfase and the de novo purine biosynthetic pathway
AU Marsilje, Thomas H.; Labroli, Marc A.; Hedrick, Michael P.; Jin, Qing; Desharnais, Joel; Baker, Stephen J.; Gooljarsingh, Lata T.; Ramcharan, Joseph; Tavassoli, Ali; Zhang, Yan; Beardsley, G. Peter; Benkovic, Stephen J.;
CS Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Bioorganic & Medicinal Chemistry (2002), 10(8), 2739-2749
CODEN: BMECEP; ISSN: 0968-0896
PB Elsevier Science Ltd.
published August 2002
DT Journal
LA English
AB The synthesis of 10-formyl-DDACTHF (I) as a potential inhibitor of glycinamide ribonucleotide transformylase (GAR Tfase) and aminoimidazole carboxamide ribonucleotide transformylase (AICAR Tfase) is reported. Aldehyde I, the corresponding γ- and α-pentaglutamates and related agents were evaluated for inhibition of folate-dependent enzymes including GAR Tfase and AICAR Tfase. The inhibitors were found to exhibit potent cytotoxic activity (CCRF-CEM IC50 for I = 60 nM) that exceeded their enzyme inhibition potency [Ki; I = 6 and 1 μM for Escherichia coli GAR and human AICAR Tfase, resp.]. Cytotoxicity rescue by medium purines, but not pyrimidines, indicated that the potent cytotoxic activity is derived from selective purine biosynthesis inhibition and rescue by AICAR monophosphate established that the activity is derived preferentially from GAR vs. AICAR Tfase inhibition. The potent cytotoxic compds. including aldehyde I lost activity against CCRF-CEM cell lines deficient in the reduced folate carrier (CCRF-CEM/MTX) or folylpolyglutamate synthase (CCRF-CEM/FPGS-) establishing that their potent activity requires both reduced folate carrier transport and polyglutamation. Unexpectedly, the pentaglutamates displayed surprisingly similar Ki's vs. E. coli GAR Tfase and only modestly enhanced Ki's vs. human AICAR Tfase. On the surface this initially suggested that the potent cytotoxic activity of I and related compds. might be due simply to preferential intracellular accumulation of the inhibitors derived from effective transport and polyglutamation (i.e., 100-fold higher intracellular concns.). However, a subsequent examination of the inhibitors against recombinant human GAR Tfase revealed they and the corresponding γ-pentaglutamates were unexpectedly much more potent against the human vs. E. coli enzyme (Ki for I, 14 nM against rhGAR Tfase vs. 6 μM against E. coli GAR Tfase) which also accounts for their exceptional cytotoxic potency.
IT 485389-59-1P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of formyldideazacyclictetrahydrofolic acid as a potent cytotoxic agent acting by selective inhibition of human GAR Tfase and de novo purine biosynthesis)
RN 485389-59-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



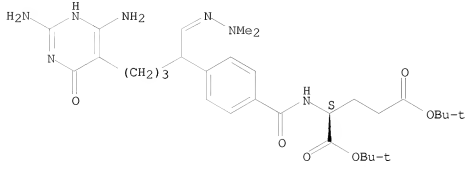
IT 136527-62-3P 485389-64-8P 485389-65-9P
485389-67-1P 485389-68-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of formyldideazacyclictetrahydrofolic acid as a potent cytotoxic agent acting by selective inhibition of human GAR Tfase and de novo purine biosynthesis)
RN 136527-62-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



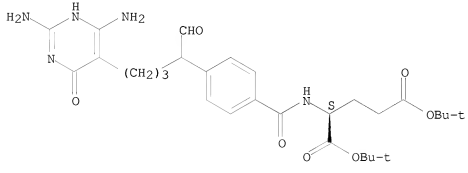
RN 485389-64-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



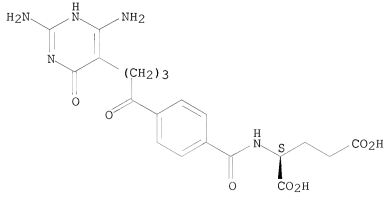
RN 485389-65-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



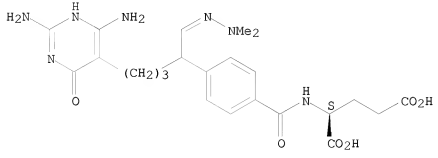
RN 485389-67-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-oxobutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 485389-68-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]- (9CI) (CA INDEX NAME)

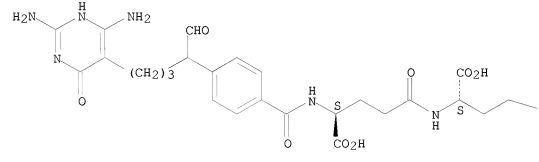
Absolute stereochemistry.
Double bond geometry unknown.



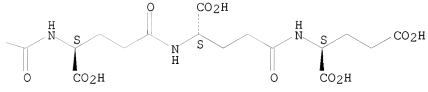
IT 485389-72-8P 485389-73-9P 485389-76-2P
485389-77-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of formyldideazacyclictetrahydrofolic acid as a potent cytotoxic agent acting by selective inhibition of human GAR Tfase and de novo purine biosynthesis)
RN 485389-72-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



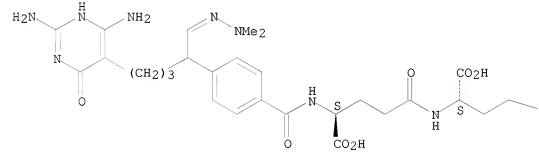
PAGE 1-B



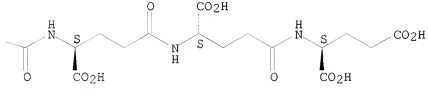
RN 485389-73-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

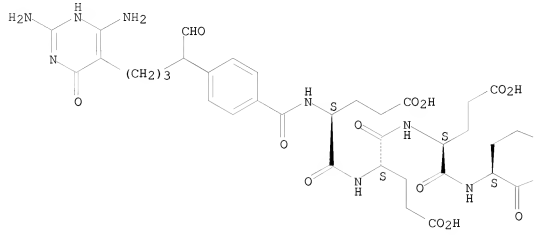


RN 485389-76-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-L-α-glutamyl-L-α-glutamyl-L-α-

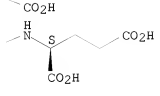
glutamyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



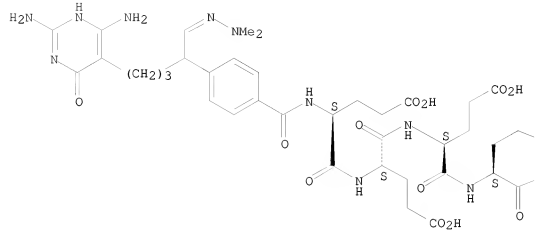
PAGE 1-B



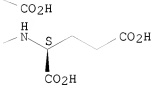
RN 485389-77-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



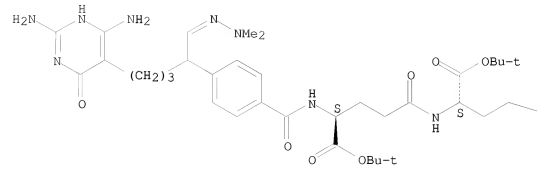
IT 485389-70-6P 485389-71-7P 485389-75-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of formyldideazacyclictetrahydrofolic acid as a potent cytotoxic agent acting by selective inhibition of human GAR Tfase and de novo purine biosynthesis)

RN 485389-70-6 CAPLUS

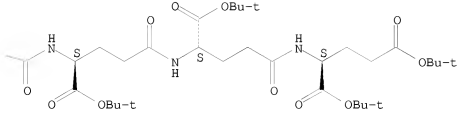
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



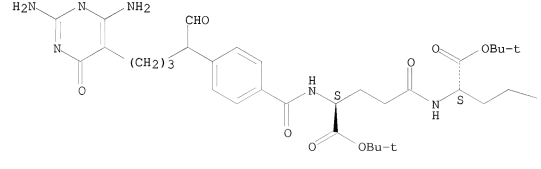
PAGE 1-B



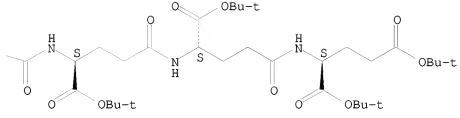
RN 485389-71-7 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-formylbutyl]benzoyl]-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



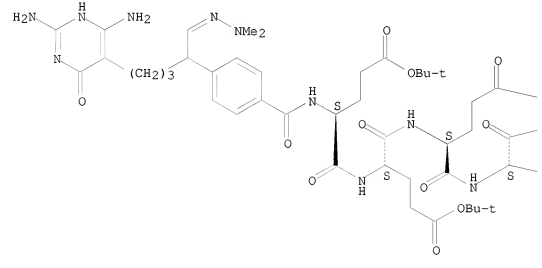
PAGE 1-B

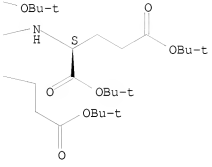


RN 485389-75-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-[(dimethylhydrazono)methyl]butyl]benzoyl]-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-L-α-glutamyl-, hexakis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

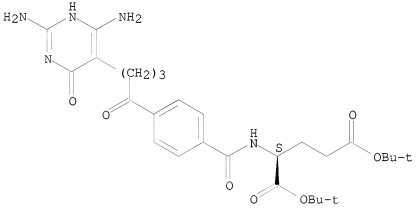
PAGE 1-A





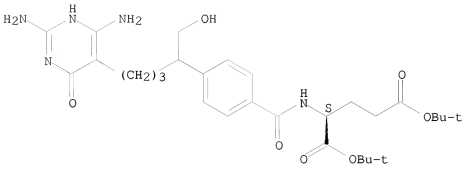
IT 485389-66-0P 485389-69-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of formyldideazacyclictetrahydrofolic acid as a potent cytotoxic agent acting by selective inhibition of human GAR Tfase and de novo purine biosynthesis)
RN 485389-66-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-oxobutyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 485389-69-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

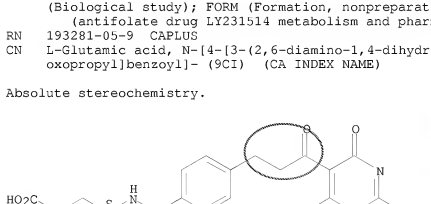
Absolute stereochemistry.



RE.CNT 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

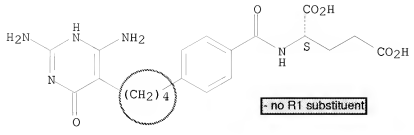
L5 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1997:414890 CAPLUS
DN 127:144690
TI Metabolism and disposition of the antifolate LY231514 in mice and dogs
AU Woodland, J. M.; Barnett, C. J.; Dorman, D. E.; Gruber, J. M.; Shih, C.; Spangle, L. A.; Wilson, T. M.; Ehlhardt, W. J.
CS Lilly Res. Laboratories, USA
SO Drug Metabolism and Disposition (1997), 25(6), 693-700
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
AB The metabolism and disposition of LY231514 was studied in mice and dogs. LY231514 is a novel pyrrolopyrimidine-based multi-target antifolate (MTA) showing broad in vivo antitumor activity in mouse models and is currently in phase II human clin. trials. Doses (i.v.) of the compound showed high plasma levels, resulting in AUC values of 30-33 μg-hr/mL for mice and dogs after 20 and 7.5 mg/kg doses, resp. The compound was eliminated rapidly. Half-life values for mice and dogs were about 7 and 2 h, resp. In vitro plasma binding measured 56% in mice, 46% in dogs, and 81% in humans. Fecal elimination was the major excretion pathway in mice after single i.v. doses of [14C]LY231514. Urine constituted the major route of excretion in dogs. Parent LY231514 accounted for the majority of urinary radiocarbon in mice (90%) and dogs (68%). Minor metabolites were found in urine, but the amts. were too small to isolate or identify. Based on an earlier observation that LY231514 photodegraded to produce reaction products having similar retention times as these minor urinary isolates, a photo oxidation system was developed which in fact produced these metabolites. Subsequently, these photolytically produced materials were used as stds. to identity two novel in vivo metabolites formed by oxidation of the pyrrolo-pyrimidine ring system of LY231514. The oxidative transformations are similar to those observed for tryptophan and other indoles in that the pyrrole ring is oxidized to give an amide; further oxidation cleaves this ring, one ring carbon is lost, and a ketone is formed.
IT 193281-05-9, LY 368962
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(antifolate drug LY231514 metabolism and pharmacokinetics in mice and dogs)
RN 193281-05-9 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-3-oxopropyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



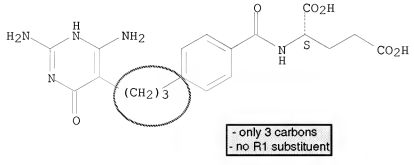
L5 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1995:786220 CAPLUS
DN 123:275185
TI Substrate specificity of mammalian folylpolyglutamate synthetase for 5,10-dideazatetrahydrofolate analogs
AU Habeck, Lillian L.; Mendelsohn, Laurane G.; Shih, Chuan; Taylor, Edward C.; Colman, Paul D.; Gossett, Lynn S.; Leitner, Tracy A.; Schultz, Richard M.; Andis, Shierri L.; Moran, Richard G.
CS Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Molecular Pharmacology (1995), 48(2), 326-33
CODEN: MOPMA3; ISSN: 0026-895X
PB Williams & Wilkins
DT Journal
LA English
AB The metabolism of 5,10-dideazatetrahydrofolate (DDATHF [lometrexol]) to polyglutamate derivs. by folylpoly-γ-glutamate synthetase (FPGS) plays a central role in the activity of this compound as an antineoplastic agent. The availability of a series of DDATHF derivs. differing in structure throughout the mol. has allowed a study of the structural requirements for substrate activity with mouse liver and hog liver FPGS. Kinetics of the polyglutamation reaction in vitro have been related to the potency of these compds. as inhibitors of the growth of human CEM leukemic cells. The structure-activity relationships for enzyme for both sources were nearly identical. FPGS from both species showed a broad acceptance for structural changes in the pyridopyrimidine ring, in the Ph group, and in the intermediate bridge region, with structural changes in these regions being reflected in changes in Km for FPGS but much more modest alterations in Vmax. The data suggested that the Ph ring was not contributing to any π-π hydrophobic interactions. It appeared to function primarily in maintaining a favorable distance between the pyridopyrimidine ring and the glutamate side chain. The lowest Km values were found for DDATHF analogs in which there were small alterations at the 10 position, e.g., 5-deazatetrahydrofolate, 10-methyl-DDATHF, and 10-formyl-5-deazatetrahydrofolate; the first-order rate consts. for these substrates were the highest in this series, an indication of the efficiency of polyglutamation at low substrate concns. After correction for the intrinsic inhibitory activity of the parent DDATH analog as an inhibitor of the target enzyme, the first-order rate consts. for FPGS were predictive of the potency of tumor cell growth inhibition for most of the compds. in this structural series.
IT 124656-55-9 169475-28-9
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(structure activity study on substrate specificity of mammalian folylpolyglutamate synthetase for dideazatetrahydrofolate analogs)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



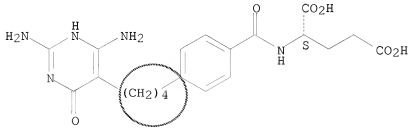
RN 169475-28-9 CAPLUS
CN L-Glutamic acid, N-[4-[3-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)propyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



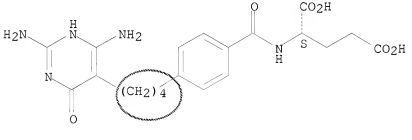
L5 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1994:315378 CAPLUS
DN 120:315378
TI Effect of purine synthesis inhibition on WiDr spheroids in vitro or on WiDr or colon 38 tumors in vivo. Complete growth inhibition but not regression
AU Jansen, Marilyn; Dykstra, Michael; Lee, Jacqueline I.; Stables, Jeremy; Topley, Peter; Knick, Vincent C.; Mullin, Robert J.; Duch, David S.; Smith, Gary K.
CS Wellcome Res. Lab., Research Triangle Park, NC, 27709, USA
SO Biochemical Pharmacology (1994), 47(6), 1067-78
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB Clin. responses for anticancer agents are based upon tumor regression. The authors have investigated the potential of glycineamide ribonucleotide transformylase (GAR TFase) inhibitors to produce regressions in multiple preclin. models of colon carcinoma. The growth of multicellular tumor spheroids of WiDr human colon carcinoma was inhibited by the GAR TFase inhibitors 5-deazaacyclotetrahydrofolate (5-DACTHF), its 2'-fluoro, 3'-fluoro, 10-deaza, and 10-thia analogs as well as 5,10-dideazatetrahydrofolate, but none of the compds. caused spheroid regressions. By contrast, complete spheroid disruption was observed with exposure to etoposide, m-AMSA (amsacrine), piritrexim, or 2-desamino-2-methyl-10-propargyl-5,8-dideazafolate (DMPDDF). Light microscopy of the spheroids treated with either 5-DACTHF or DMPDDF suggested that the reason for the difference is extensive cell kill throughout the spheroid in the presence of DMPDDF compared with little or no kill, over that found in controls, with 5-DACTHF. Treatment of spheroids with 5-DACTHF in the presence of 1 μM hypoxanthine resulted in no significant reversal of growth inhibition; 50% reversal required 10 μM hypoxanthine. The spheroid studies were extended to in vivo studies examining the effects of 5-DACTHF on established WiDr and colon 38 tumors. The results showed that, in contrast to melphalan, which produced cures and tumor regressions, 5-DACTHF produced reversible growth inhibition with no significant regression of tumors. The results predict that clin. response, typically measured by tumor regression, may be rare following single agent therapy with inhibitors of de novo purine biosynthesis.
IT 124656-55-9, 662U88
RL: BIOL (Biological study)
(colon tumor of humans inhibition by)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



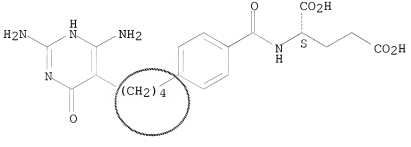
L5 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:400409 CAPLUS
DN 117:409
TI In vivo antitumor activity and metabolism of a series of 5-deazaacyclotetrahydrofolate (5-DACTHF) analogs
AU Mullin, Robert J.; Keith, Barry, R.; Bigham, Eric C.; Duch, David S.; Ferone, Robert; Heath, Louise S.; Singer, Sara; Waters, Kathleen A.; Wilson, H. Robert
CS Wellcome Res. Lab., Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA
SO Biochemical Pharmacology (1992), 43(7), 1627-34
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB This study compares the antitumor activity and metabolism of the purine de novo biosynthesis inhibitor 5-deazaacyclotetrahydrofolate (I; Z = NH, R = H, R1 = H)and a series of analogs. All compds. have similar IC50 values for inhibition of MCF-7 cell growth, activity of glycineamide ribonucleotide transformylase, and methotrexate uptake by MOLT-4 cells, the latter a measure of cellular uptake potential. Only 5-deazaacyclotetrahydrofolate and the 2'-fluoro (I; Z = NH, R = H, R1 = F) and 3'-fluoro (I; Z = NH, R = F, R1 = H) analogs demonstrated significant inhibition of colon 38 adenocarcinoma or HCT-116 colon carcinoma growth in vivo. This correlated with the Km of these compds. for folylpolyglutamate synthetase. 5-Deazaacyclotetrahydrofolate and 2'-fluoro-5-deazaacyclotetrahydrofolate, which displayed the strongest antitumor activity, were detectable in colon 38 tumor tissue 24 h after dosing and were present nearly exclusively as the polyglutamated species. These results indicate that polyglutamation represents a critical step in the in vivo antitumor activity of these compds.
IT 124656-55-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, against human and murine colon cancer, polyglutamation in)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



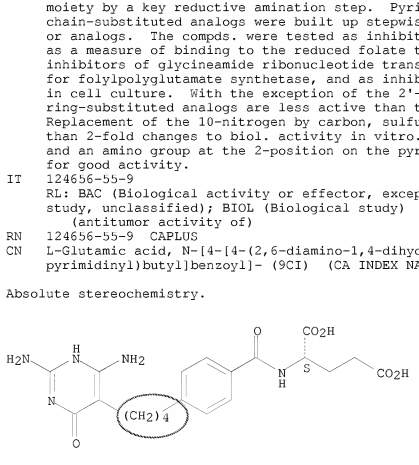
L5 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:236113 CAPLUS
DN 116:236113
TI Novel 5-desmethylene analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid as potential anticancer agents
AU Taylor, Edward C.; Gillespie, Paul; Patel, Mona
CS Dep. Chem., Princeton Univ., Princeton, NJ, 08544, USA
SO Journal of Organic Chemistry (1992), 57(11), 3218-25
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA English
AB The synthesis and biol. activity of novel 5-desmethylene analogs I (R = H, n = 3, 4; R = CHO, n = 4) and II [R = H, R1 = OMe, Z = (CH2)3, CH2CH2C.tplbond.C; R = H, R1 = Cl, Z = CH2C.tplbond.C, (CH2)3, (CH2)4; R = CHO, R1 = Cl, Z = CH2CH2C.tplbond.C] of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, Lometrexol), a potent antitumor agent presently undergoing clin. trials, are described. I are representative of a new series of optically pure analogs of DDATHF.
IT 124656-55-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antitumor activity of)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



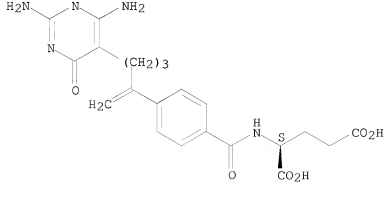
L5 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:194810 CAPLUS
DN 116:194810
TI Synthesis and biological activity of open-chain analogs of 5,6,7,8-tetrahydrofolic acid-potential antitumor agents
AU Bigham, Eric C.; Hodson, Stephen J.; Mallory, W. Revill; Wilson, David; Duch, David S.; Smith, Gary K.; Ferone, Robert
CS Wellcome Res. Lab., Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA
SO Journal of Medicinal Chemistry (1992), 35(8), 1399-410
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 116:194810
AB The synthesis and in vitro antitumor activity of inhibitors, e.g. I (n = 3, R = H, n = 4, R = NH2, Y = NH, Z = H; n = 3, R = NH2, Y = S, O, CH2, CH2, Z = H; n = 3, R = NH2 Y = NH, Z = 3-F, 2-F, 3-Me, 3-MeO, 2-Cl), of purine de novo biosynthesis that are analogs of 5-deazaacyclotetrahydrofolic acid I (n = 3, R = NH2, Y = NH, Z = H) are described. Benzene ring-substituted analogs were synthesized from a protected pyrimidinylpropionaldehyde and a substituted benzoyl glutamate moiety by a key reductive amination step. Pyrimidine and linking chain-substituted analogs were built up stepwise from p-aminobenzoic acid or analogs. The compds. were tested as inhibitors of methotrexate uptake as a measure of binding to the reduced folate transport system, as inhibitors of glycineamide ribonucleotide transformylase, as substrates for folylpolyglutamate synthetase, and as inhibitors of tumor cell growth in cell culture. With the exception of the 2'-fluoro substituent, the ring-substituted analogs are less active than the parent compound Replacement of the 10-nitrogen by carbon, sulfur, or oxygen produced less than 2-fold changes to biol. activity in vitro. A 4-atom linking chain and an amino group at the 2-position on the pyrimidine ring are important for good activity.
IT 124656-55-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antitumor activity of)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



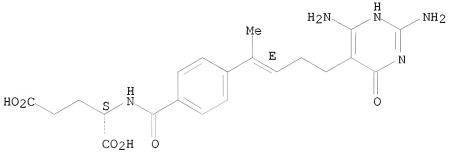
L5 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:152317 CAPLUS
DN 116:152317
TI Synthesis of 10-substituted "open-chain" analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, lometrexol)
AU Taylor, Edward C.; Schrader, Thomas H.; Walensky, Loren D.
CS Dep. Chem., Princeton Univ., Princeton, NJ, 08544, USA
SO Tetrahedron (1992), 48(1), 19-32
CODEN: TETRAB; ISSN: 0040-4020
same as #21
DT Journal
LA English
OS CASREACT 116:152317
AB Several novel and very potent folate antimetabolites, e.g. I [R = Me, CH2OH, CH2B(OH)2] and II, structurally based on a previously described open-chain version (Taylor, E. C.; Harrington, P. M., 1989) of DDATHF but carrying 1-carbon substituents in the 10-position, have been synthesized. A key synthetic sequence involving a palladium-catalyzed C-C coupling reaction, oxymercuration, and Wittig olefination constitutes a new route to α-branched 4-styrene carboxylic acids. Classical construction of the pyrimidine ring from the key intermediate AcOCH2CH2CH2C(:CH2)C6H4CO2Me-4 followed by glutamate coupling and hydrolysis furnished the 10-methenyl derivative II. The 10-methenyl functionality in II was further modified to afford the 10-methyl-, 10-hydroxymethyl- and 10-dihydroxyboromethyl derivs. I; double bond isomerization led to the 10-methyl-9,10-didehydro analog. Preliminary in vitro cell culture screening showed that many of these "open-chain" analogs rivaled DDATHF itself as cytotoxic agents, and were about ten times more active than the parent "open-chain" DDATHF analog I (R = H). Surprisingly, however, compds. II and I (R = Me) were inactive in vivo.
IT 136527-59-8P 139577-60-9P 139577-65-4P
139577-66-5P 139577-67-6P 139577-68-7P
139630-32-3P 139630-33-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of)
RN 136527-59-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylenebutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



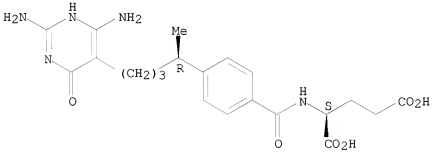
RN 139577-60-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methyl-1-butenyl]benzoyl]-, (E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



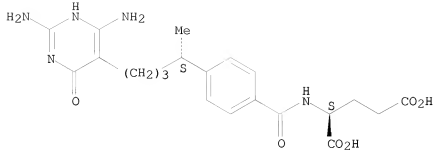
RN 139577-65-4 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylbutyl]benzoyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



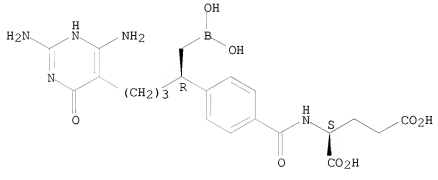
RN 139577-66-5 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylbutyl]benzoyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



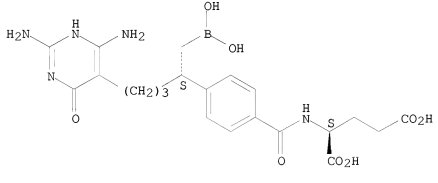
RN 139577-67-6 CAPLUS
CN L-Glutamic acid, N-[4-[1-(boronomethyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



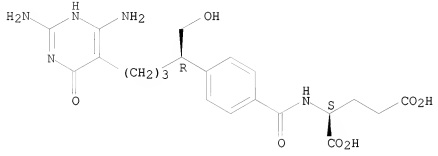
RN 139577-68-7 CAPLUS
CN L-Glutamic acid, N-[4-[1-(boronomethyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



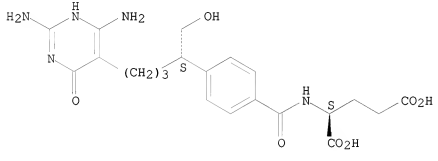
RN 139630-32-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



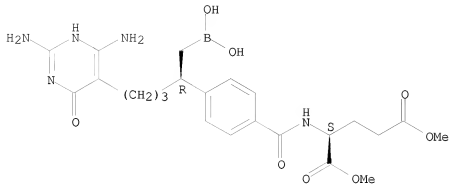
RN 139630-33-4 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



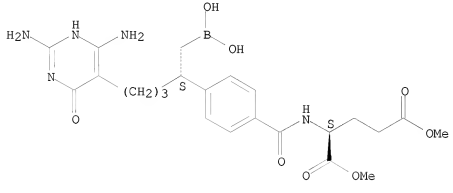
IT 139577-63-2P 139577-64-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and hydrolysis reactions of)
RN 139577-63-2 CAPLUS
CN L-Glutamic acid, N-[4-[1-(boronomethyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, 1,5-dimethyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



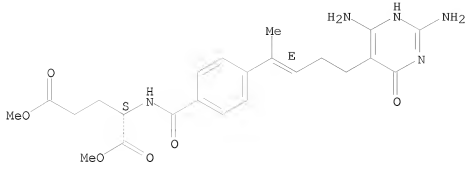
RN 139577-64-3 CAPLUS
CN L-Glutamic acid, N-[4-[1-(boronomethyl)-4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, 1,5-dimethyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



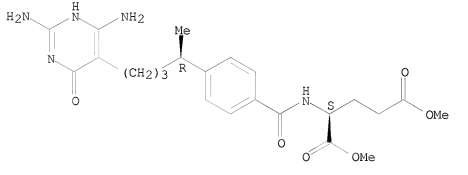
IT 139577-59-6P 139577-61-0P 139577-62-1P
139630-30-1P 139630-31-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)
RN 139577-59-6 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methyl-1-butenyl]benzoyl]-, dimethyl ester, (E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



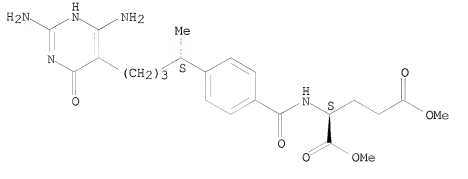
RN 139577-61-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylbutyl]benzoyl]-, dimethyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139577-62-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylbutyl]benzoyl]-, dimethyl ester, (S)- (9CI) (CA INDEX NAME)

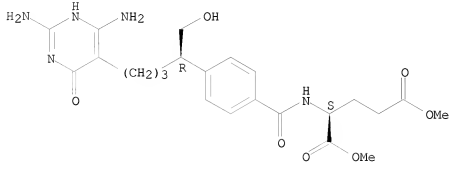
Absolute stereochemistry.



RN 139630-30-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-

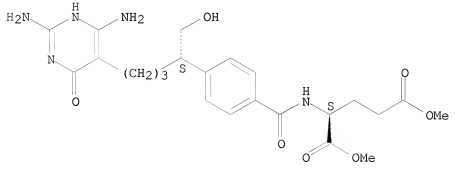
(hydroxymethyl)butyl]benzoyl]-, dimethyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



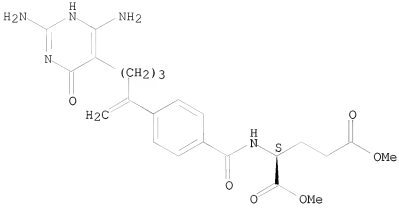
RN 139630-31-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, dimethyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



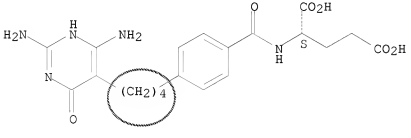
IT 136548-01-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, reduction, hydroboration, or saponification of)
RN 136548-01-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylenebutyl]benzoyl]-, dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:151700 CAPLUS
DN 116:151700
TI Synthesis and biological activity of acyclic analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid
AU Shih, Chuan; Gossett, Lynn S.; Worzalla, John F.; Rinzel, Sharon M.; Grindey, Gerald B.; Harrington, Philip M.; Taylor, Edward C.
CS Lilly Corp. Cent., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Journal of Medicinal Chemistry (1992), 35(6), 1109-16
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 116:151700
AB Analogs of N-[4-[4-(2,4-diamino-1,6-dihydro-6-oxo-5-pyrimidinyl)butyl]benzoyl]-L-glutamic acid (7-DM-DDATHF) (I) were prepared I is an acyclic modification of the folate antimetabolite 5,10-dideazatetrahydrofolic acid (DDATHF). The analog II was prepared Cell culture culture toxicity studies against human lymphoblastic leukemic cells gave values for IC50 of 0.042-48 μM for the I analogs tested. I had moderate in vivo activity against 6C3HED lymphosarcoma and mammary adenocarcinoma.
IT 124656-55-9DP, analogs
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as neoplasm inhibitors)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

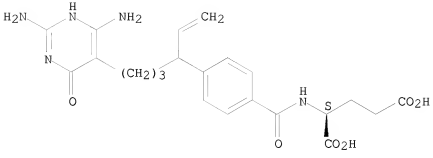


L5 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1991:583953 CAPLUS
DN 115:183953
TI Preparation of substituted N-[4-(pyrimidin-5-ylalkyl)benzoyl]-L-glutamic acid derivatives as antineoplastic agents
IN Taylor, Edward C.; Schrader, Thomas H.; Walensky, Loren D.
PA Princeton University, USA
SO U.S., 8 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5013738	A	19910507	US 1990-510669	19900418
	CA 2037015	A1	19911019	CA 1991-2037015	19910225
	JP 05262746	A	19931012	JP 1991-65397	19910306
	EP 452660	A2	19911023	EP 1991-103482	19910307
	EP 452660	A3	19920129		
	EP 452660	B1	19960529		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	AT 138655	T	19960615	AT 1991-103482	19910307
PRAI	US 1990-510669	A	19900418		

OS CASREACT 115:183953; MARPAT 115:183953
AB Title compds. L-I (R = H2C:CH, HOCH2; R2, R3 = H, carboxy-protecting group ; Z = H, ZR = CH2; n = 2-5) and a salt thereof, are prepared 4-[6-(2,6-Diamino-4-hydroxypyrimidin-5-yl)hex-1-en-3-yl]benzoic acid (preparation given), N-methylmorpholine and DMF were vigorously stirred at ambient temperature, to this solution was added 2,4-dimethoxy-6-chloro-1,3,5-triazine, the mixture stirred at room temperature followed by addition of di-Me L-glutarate-HCl to give after workup I (R = H2C:CH, R2 = R3 = Me, Z = H, n =3) which in aqueous NaOH was stirred overnight to form the di-Na salt to which was added AcOH to give I (R = H2C:CH, R2 = R3 = Z = H, n = 3) (II). The IC50 of II in whole cell human leukemia cell lines CCFR-CEM was .apprx.0.0035 μg/mL.
IT 136527-51-0P 136527-60-1P 136527-63-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and neutralization of)
RN 136527-51-0 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-ethenylbutyl]benzoyl]-, disodium salt (9CI) (CA INDEX NAME)

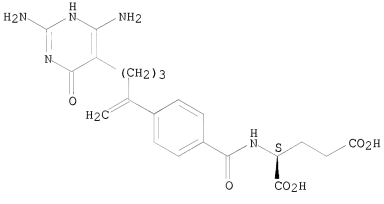
Absolute stereochemistry.



●2 Na

RN 136527-60-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylenebutyl]benzoyl]-, disodium salt (9CI) (CA INDEX NAME)

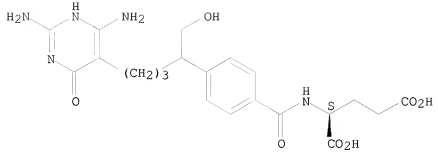
Absolute stereochemistry.



●2 Na

RN 136527-63-4 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, disodium salt (9CI) (CA INDEX NAME)

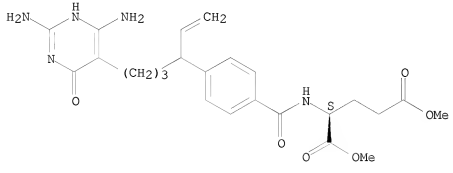
Absolute stereochemistry.



●2 Na

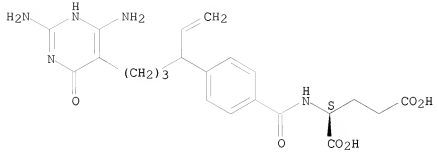
IT 136527-49-6P 136527-50-9P 136527-59-8P
136527-61-2P 136527-62-3P 136548-01-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antineoplastic agent)
RN 136527-49-6 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-ethenylbutyl]benzoyl]-, dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



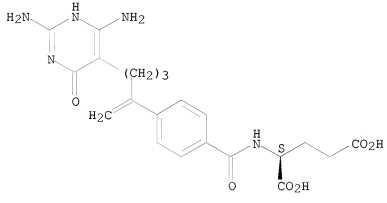
RN 136527-50-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-ethenylbutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



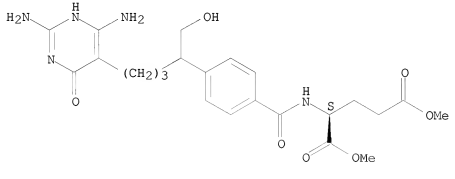
RN 136527-59-8 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylenebutyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 136527-61-2 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]-, dimethyl ester (9CI) (CA INDEX NAME)

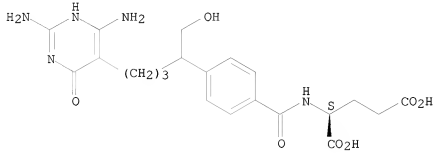
Absolute stereochemistry.



RN 136527-62-3 CAPLUS

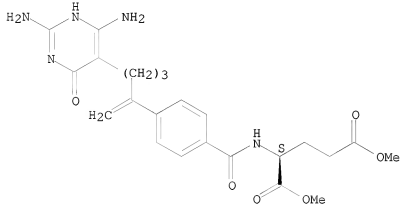
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-(hydroxymethyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



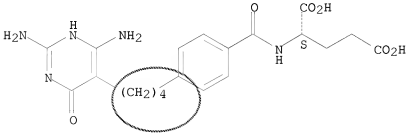
RN 136548-01-1 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)-1-methylenebutyl]benzoyl]-, dimethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



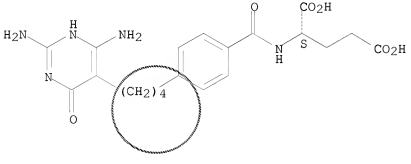
L5 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1991:492922 CAPLUS
DN 115:92922
TI Monocyclic 5-deazatetrahydrofolate analogs as inhibitors of de novo purine biosynthesis
AU Bigham, E.; Duch, D.; Ferone, R.; Kelley, J.; Smith, G.
CS Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA
SO Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folic Acid Deriv., 9th (1990), Meeting Date 1989, 961-4. Editor(s): Curtius, Hans-Christoph; Ghisla, Sandro; Blau, Nenad. Publisher: de Gruyter, Berlin, Fed. Rep. Ger.
CODEN: 57FTAQ
DT Conference
LA English
AB A report from a symposium on the preparation and antitumor activity of the title analogs I [R = H, Z = NH, n = 3; R = NH2, Z = NH, n = 2-4; Z = CH2, NMe, N(CHO), n = 3].
IT 124656-55-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, antitumor activity, and inhibition by, of purine biosynthesis)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



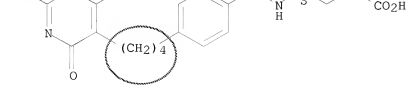
L5 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1991:492863 CAPLUS
DN 115:92863
TI Synthesis and structure-activity relationship studies of 5,10-dideazatetrahydrofolic acid (DDATHF)
AU Shih, C.; Grindey, G. B.; Gossett, L. S.; Moran, R. G.
CS Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Chem. Biol. Pteridines, 1989 Proc. Int. Symp. Pteridines Folic Acid Deriv., 9th (1990), Meeting Date 1989, 1035-8. Editor(s): Curtius, Hans-Christoph; Ghisla, Sandro; Blau, Nenad. Publisher: de Gruyter, Berlin, Fed. Rep. Ger.
CODEN: 57FTAQ
DT Conference
LA English
AB A report from a symposium on the growth inhibitory activity of the title analogs I [R = L-Glu-OH, D-Glu-OH, L-Phe-OH, DL-Asp-OH, L-Glu(NEt2)-NEt2, Z = CH2CH2C6H4-p; R = L-Glu-OH, Z = CH2CH2Z1, (CH2)n, CH2NH; Z1 = 2-chloro-1,4-phenylyl, 2-fluoro-1,4-phenylyl, 2,5-thienylyl, 1,4-cyclohexylyl; n = 3-6] and II.
IT 124656-55-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



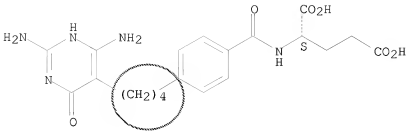
L5 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1991:484943 CAPLUS
DN 115:84943
TI Induction of HL-60 leukemia cell differentiation by tetrahydrofolate inhibitors of de novo purine nucleotide biosynthesis
AU Sokoloski, John A.; Beardsley, G. Peter; Sartorelli, Alan C.
CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SO Cancer Chemotherapy and Pharmacology (1991), 28(1), 39-44
CODEN: CCPHDZ; ISSN: 0344-5704
DT Journal
LA English
AB 5,10-Dideazatetrahydrofolic acid (DDATHF) is a folate antimetabolite that shows activity against glycinamide ribonucleotide (GAR) transformylase, a folate-requiring enzyme in the de novo purine nucleotide biosynthetic pathway. Previous studies have shown that DDATHF is an effective inducer of the maturation of HL-60 promyelocytic leukemia. In solution, DDATHF is a mixture of two diastereomers due to an asym. configuration at carbon 6. Incubation of HL-60 cells with each diastereomer resulted in an inhibition of cellular proliferation after 48 h that preceded an increase in the number of differentiated myeloid cells. Several analogs of DDATHF were also tested as inducers of the differentiation of HL-60 cells. With the exception of the 10-acetyl analog of 5-deazatetrahydrofolic acid, all compds. displayed similar activities as inducers of maturation. The finding that both stereoisomers of DDATHF, as well as the analogs tested, could selectively reduce intracellular purine nucleotide levels suggested that these compds. inhibited purine nucleotide biosynthesis de novo. This possibility was confirmed by the finding that hypoxanthine completely prevented the reduction of intracellular purine nucleotide levels, as well as the induction of differentiation and the inhibition of cellular growth, by these folate analogs. The results suggest that GAR transformylase is a target for a series of compds. whose structures resemble that of tetrahydrofolate and indicate that the inhibition of GAR transformylase by these compds. is sufficient to induce the maturation of HL-60 leukemia cells.
IT 124656-55-9
RL: BIOL (Biological study)
(leukemia cell differentiation induced by, inhibition of purine nucleotide formation in)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



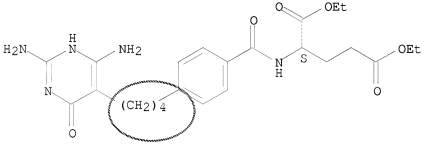
L5 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1991:94633 CAPLUS
DN 114:94633
TI Structural features of 5,10-dideaza-5,6,7,8-tetrahydrofolate that determine inhibition of mammalian glycinamide ribonucleotide formyltransferase
AU Baldwin, Samuel W.; Tse, Archie; Gossett, Lynn S.; Taylor, Edward C.; Rosowsky, Andre; Shih, Chuan; Moran, Richard G.
CS Norris Compr. Cancer Cent., Univ. South. California, Los Angeles, CA, 90033, USA
SO Biochemistry (1991), 30(7), 1997-2006
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The structural features of 5,10-dideaza-5,6,7,8-tetrahydrofolate (I) that determine the activity of this compound as an inhibitor of glycinamide ribonucleotide formyltransferase (GARFT) purified from mouse L1210 cells were examined 5-Deazatetrahydrofolate was as good an inhibitor of GARFT as I, indicating that isosteric replacement of N by C at the 5-position of tetrahydrofolate is sufficient for inhibition of GARFT. 5,10-Dideazafolic acid, 5,8,10-trideazatetrahydrofolate, and 2-desamino-5,10-dideazatetrahydrofolate were poor inhibitors of GARFT, indicating that a reduced pyridopyrimidine ring, N-8, and the 2-amino group of I, resp., play an important role in the binding of tetrahydrofolate analogs to this enzyme. I analogs in which the Ph ring was replaced either by a cyclohexyl ring or by methylene groups retained activity as inhibitors. 5,10-Dideazatetrahydrohomofolate was about 6 times more potent as an inhibitor of GARFT than I, but 5,10-dideazatetrahydronorfolate had about one-sixth of the activity of I. An analog of I in which the glutamic acid side chain was replaced by aspartic acid (which was not a substrate for polyglutamation and was only weakly cytotoxic) was equiactive with DDATHF as an inhibitor of purified GARFT. Surprisingly, 5,10-dideazatetrahydropteroic acid was about as active as I as an inhibitor of GARFT, an indication that the glutamic acid in the side chain of DDATHF does not play a role in this ligand-enzyme interaction. The polyglutamate derivs. of I bound up to 100 times tighter to GARFT than I itself; longer chain polyglutamates conformed to Goldstein's zone B behavior under exptl. conditions and were projected to be in zone C, i.e., stoichiometric inhibition, in vivo. It is concluded that the presence of C at the 5-position of tetrahydrofolate analogs is sufficient for inhibition of GARFT, that N-8 and the 2-amino group are involved in binding of I to GARFT, probably through H bonds, and that the structures of the Ph ring and amino acid side chain of I analogs are not primary determinants of GARFT inhibition by monoglutamate forms of these compds. Also polyglutamation plays a major role in the potent cytotoxicity of DDATHF.
IT 124656-55-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(glycinamide ribonucleotide formyltransferase-inhibiting activity of)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



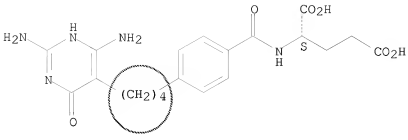
L5 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1990:99168 CAPLUS
DN 112:99168
TI A facile route to "open chain" analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF)
AU Taylor, Edward C.; Harrington, Philip M.; Shih, Chuan
CS Dep. Chem., Princeton Univ., Princeton, NJ, 08544, USA
SO Heterocycles (1989), 28(2), 1169-78
CODEN: HTCYAM; ISSN: 0385-5414
DT Journal
LA English
OS CASREACT 112:99168
AB [[(Oxopyrimidin-5-yl)butyl]benzoyl-L-glutamic acid derivative I (R = OH, R1 = NH2, R2 = Glu-OH) is a representative of a new series of achiral analogs of the potent anticancer agent 5,10-dideaza-5,6,7,8-tetrahydrofolic acid. Members of this open chain pyrimidine series, I (R = OH, R1 = NH2, Me; R = R1 = NH2; R2 = Glu-OH), were synthesized via guanidine cyclization of 4-MeO2CC6H4(CH2)4CHR3R4 (R3 = CO2Et, R4 = CN, COMe; R3 = R4 = CN) to give the pyrimidines I (R, R1 = same; R2 = OMe). Ester hydrolysis, glutamate coupling, and final saponification yielded the target compds.
IT 124656-59-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)
RN 124656-59-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, diethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 124656-55-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as folate antimetabolite)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

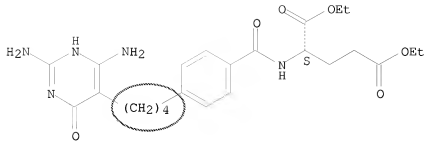


L5 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1990:56690 CAPLUS
DN 112:56690
TI Preparation and testing of N-[(aminopyrimidinyl)acyl]glutamates as neoplasm inhibitors
IN Taylor, Edward C.; Harrington, Philip M.; Shih, Chuan
PA Princeton University, USA; Eli Lilly and Co.
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 325343	A2	19890726	EP 1989-300045	19890105
	EP 325343	A3	19900905		
	EP 325343	B1	19940622		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	US 4871743	A	19891003	US 1988-144970	19880119
	ES 2055024	T3	19940816	ES 1989-300045	19890105
	CA 1314547	C	19930316	CA 1989-588039	19890112
	JP 02000781	A	19900105	JP 1989-10979	19890119
PRAI	US 1988-144970	A	19880119		

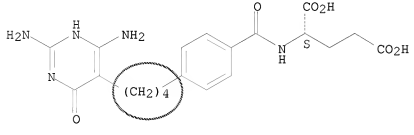
OS CASREACT 112:56690; MARPAT 112:56690
AB The title compds. [I; X, Y = OH, amino; Z = (F- or Cl-substituted) 1,4-phenylene, cyclohexa-1,4-diyl, C2-5 alkylene; n = 2-6], useful as neoplasm inhibitors and for treating mycosis fungoides, psoriasis, and arthritis, were prepared Thus, guanidine and Me 4-(5-carboethoxy-5-cyanopentyl)benzoate (preparation given) were stirred 12 h in DMF with gentle heating to give Me 4-[4-(2,4-diamino-6-hydroxypyrimidin-5-yl)butyl]benzoate, which was stirred 18 h in 1N NaOH with gentle heating followed by acidification with HOAc to give the free acid. The latter was stirred with N-methylmorpholine and Ph N-phenylphosphoramidochloridate in N-methylpyrrolidone for 1 h followed by addition of di-Et L-glutamate hydrochloride and stirring for 24 h. The coupling product was hydrolyzed by stirring in 1N hydroxide for 72 h followed by acidification with HCl to give L-I (X = OH, Y = NH2, Z = 1,4-phenylene, n = 4) (II). II had an IC50 of 0.0632 μ/gmL against CCRF-CEM cells. I may be administered at higher doses than methotrexate.
IT 124656-59-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for neoplasm inhibitor)
RN 124656-59-3 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]-, diethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 124656-55-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as neoplasm inhibitor)
RN 124656-55-9 CAPLUS
CN L-Glutamic acid, N-[4-[4-(2,6-diamino-1,4-dihydro-4-oxo-5-pyrimidinyl)butyl]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                   -21.60      -21.60

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